REMARKS

This submission is in response to the non-final Office Action mailed January 23, 2006. Claims 1-41 are pending. Claims 25-39 have been withdrawn from consideration. Claims 1-24, 40 and 41 stand rejected. Claims 1 and 11 have been amended to particularly point out what applicants regard as the present invention. Support for Claims 1 and 11 as amended can be found, for example, in original Claims 12-15 and 18. Claims 12-15, and 19 have been amended to delete confusing and/or superfluous text. Claims 25, 30, 31, 32, 38, and 39 have been amended to recite the concentration of specific preservative, as per claim 11. Claims 32, 38 and 39 have also been amended to recite that the method is for producing "anesthesia", in accordance with the recitation in the body of the claim of administering an anesthetically effective amount of ketamine. Claim 18 has been cancelled without prejudice or disclaimer. No new matter has been introduced by way of this amendment. Reconsideration is respectfully requested.

I. Restriction Requirement

The Examiner has required restriction of the claims to one of the following Groups under 35 U.S.C. § 121:

Group I:	Claims 1-24 and 40-41, drawn to a composition comprising NMDA antagonist and preservative in a suitable carrier; and
Group II:	Claims 25-39, drawn to a process of using said composition.

The Applicants hereby elect, with traverse, to prosecute the claims of Group I which are directed to a composition comprising NMDA antagonist and preservative. Although Applicants are making the above election to be fully responsive to the Restriction Requirement, Applicants respectfully traverse the Requirement and reserve the right to petition under 37 C.F.R. § 1.144. In particular, Applicants respectfully request reconsideration and withdrawal of the Restriction Requirement to allow prosecution of all claim groups in the present application, for the reasons provided below. In any event, the method claims should be rejoined with allowed composition claims, provided that the method claims are of the same scope of the composition claims, as discussed below.

Species Election

The Examiner has further required election of a species of one of the following preservative groups under 35 U.S.C. § 121:

(i) Organic acids or esters;

(ii) Alcohols, polyols, and phenols;

(iii) Alkyl parabens;

(iv) Cresols; or

(v) Benzalkonium chloride, chlorhexidine, imidurea, alpha tocopherol and EDTA.

Applicants hereby elect the species of Group (v). As indicated by the examiner, claims 1 and 10-22 read on this election. Additionally, withdrawn claims 25-29 and 32-37 read on this election. Applicants make these elections of species to be fully responsive to the species election requirement.

Pursuant to MPEP section 809.02(a) upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. Accordingly, Applicants submit that upon allowance of the generic claims, all the remaining non-elected claims must be considered.

Rejoinder of Group II

Applicants respectfully reserve their right to rejoinder of the non-elected claims prior to a notice of allowance for the elected claims of Group I in accordance with the guidance given by the Commissioner of Patents and Trademarks in 1184 OG 86. See also *In re Ochiai*, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 37 USPQ2d 1663 (Fed. Cir. 1996), where the Federal Circuit held that where an otherwise conventional process was patentable if it made or used novel nonobvious products in the claimed processes. See also MPEP 821.04(b), which states,

> ... if applicant elects a claim(s) directed to a product which is subsequently found allowable, withdrawn process claims which depend from or otherwise require all the limitations of an allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must depend from or otherwise require all the limitations of an allowable product claim for that process invention to be rejoined.

Applicants respectfully submit that the withdrawn process claims have been amended to include all of the limitations of the product claim and accordingly should be rejoined upon allowance of the product claims.

II. Information Disclosure Statement

The Examiner has noted that the IDS filed March 24, 2004 improperly listed the International Search Report (ISR). Applicants have clarified with the Examiner that the ISR should not be listed on the IDS form in addition to the individual references. It is Applicants understanding that no further action is necessary in this regard.

III. Rejections under 35 U.S.C. § 102(b)

A. Claims 1, 10, 11, and 17 stand rejected as anticipated under 35 U.S.C. § 102(b) by WO 98/51282 (Unger).

Claims 1, 10, 11, and 17 stand rejected as anticipated under 35 U.S.C. § 102(b) by WO 98/51282 (Unger). According to the Examiner, Unger teaches a pharmaceutical composition comprising a therapeutic, such as an anesthetic agent, in combination with a surfactant, in an aqueous medium. The Examiner concedes that although the claimed composition is not named, one skilled in the art, based on the disclosure, could select the proper constituents named in the lists of alternatives to arrive at the claimed invention. According to the Examiner, the various substituents are "well delineated" and "sufficiently limited" for one skilled in the art to "at once envisage" the claimed product from the number of alternative compounds disclosed in Unger. Further, the Examiner concedes that the reference does not teach the lack of neurotoxicity, but instead states that the feature is inherent to the composition and need not be explicitly recited. Applicants respectfully traverse the rejection and request reconsideration.

Applicants submit that in order for a reference to anticipate under § 102(b), the reference must disclose each and every limitation of the claimed invention, and must be an embodiment of the claimed invention. *Dana Corp. v. Am. Axle & Mfg., Inc.*, 61 USPQ2d 1609 (Fed. Cir. 2002) (emphasis added). The teaching must clearly disclose the invention with a certain degree of precision, without the need for picking and choosing components. *Ex parte Westphal*, 223 USPQ

630 (Bd. Pat. App. 1983) (emphasis added). The Court of Customs and Patent Appeals has counseled against "the mechanistic dissection and recombination of the components of the specific illustrative compounds in every chemical reference containing them, to create hindsight anticipations with the guidance of an applicant's disclosures, on the theory that such reconstructed disclosures describe specific compounds within the meaning of section 102." *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

Applicants point out that the Examiner concedes that Unger fails to disclose the combination of features recited in the claimed invention. As such, Unger requires one skilled in the art to pick and choose components. In doing so, Applicants submit that Unger fails to anticipate the claimed invention.

Unger teaches solid porous matrices having a surfactant, solvent, and a bioactive agent. According to the Examiner, Unger's teaching of a surfactant such as alkyl dimetheylbenzylammonium chloride (a.k.a. benzalkonium chloride) (page 19, lines 7-8), and therapeutic agents including ketamine (page 44), anticipates the claimed invention. Contrary to the Examiner's statement that the number of alternatives for active ingredients is "about 14 compounds", and that the suitable surfactants is "about 31 agents", Applicants submit that Unger discloses a far greater number of surfactant alternatives and active agent alternatives. Unger's disclosure regarding surfactants begins on page 18 of the specification, and proceeds to span over 20 pages of the description including numerous examples of lipids, oils, fluorosurfactants, proteins, polymers, fluorinated compounds, among others, some of which exemplify over 50 "suitable" agents in a particular category. Unger's disclosure regarding active agents begins on page 41 of the disclosure and also spans numerous pages reciting pages of exemplary types of compounds. The Examiner has arbitrarily reduced scores of alternatives to "about 14 compounds" and "about 31 agents", and then has selectively chosen categorical compounds to shoe-horn this reference into the case law on anticipation. However, the law is clear and there is no basis to select the specific compounds, or category, in their specific combination to arrive at the claimed invention.

Unger does not teach the composition with the specific combination of an NMDA receptor antagonist and benzalkonium chloride preservative as claimed in claims 10, 11 or 17. One skilled in

the art must pick and choose components from the list of potential ingredients disclosed in Unger to arrive at the present invention.

With respect to claim 1, Unger is completely silent to the fact that the claimed invention results in a composition that does not cause any significant neurotoxicity, and as exemplified by the unexpectedly improved neurotoxicity profile compared to formulations of ketamine with benzethenium chloride. As such, Applicants submit that Unger fails to teach each and every limitation of the presently claimed invention and therefore is not anticipatory prior art. Accordingly, the rejection should be withdrawn.

B. Claims 1, 10, 17, 18, and 21 stand rejected as anticipated under 35 U.S.C. § 102(b) by Collier et al. (WO 00/24396).

Claims 1, 10, 17, 18 and 21 stand rejected as anticipated under 35 U.S.C. § 102(b) by Collier et al. (WO 00/24396). According to the Examiner, Collier teaches a composition comprising an NMDA receptor antagonist (e.g., eliprodil and ifenprodil) with a preservative (e.g., benzalkonium chloride) in amounts ranging from 0.01% to 5% by weight, preferably 0.01%. Applicants traverse the rejection and respectfully request reconsideration.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants submit that Collier is directed to the treatment of disorders of the outer retina which require particular formulations having specific dosage amounts. Specifically, Collier discloses the use of certain glutamate antagonists with a preservative in effective amounts to treat such ocular or ophthalmic disorders. However, applicants submit that Collier fails to teach formulations having anesthetically or analgesically effective amounts of NMDA receptor antagonists combined with a preservative, to yield a composition with reduced neurotoxicity, as claimed. Therefore, Collier cannot anticipate the claimed invention.

Collier's Examples 1 and 2 disclose the use of memantine, eliprodil, and MK-801 (dizocilpine); however, Collier is entirely silent as to their preparation or formulation. Based on the specification, there is no clear indication as to what formulation is being used or with what preservative. One skilled in the art would recognize that each of these drugs is commercially available, however none of the products are commercially formulated with a preservative so as to

yield a composition with reduced neurotoxicity as recited by the claims. Indeed, MK-801 has been shown to be neurotoxic, so the issue of formulating a composition of the invention with reduced neurotoxicity is nowhere in Collier. Neither Example 1 or 2 discloses nor suggests the combination of an NMDA receptor antagonist with a preservative.

The Examiner has referenced Collier's Examples 3 and 6 as specifically anticipating the claimed invention. However, applicants submit that neither Example teaches the presently claimed invention. Example 3 provides a formulation for a 1.0% eliprodil suspension w/v%, wherein the constituents include 1% eliprodil (e.g. 1 mg/ml) and 0.01% benzalkonium chloride. The suspension also includes hydroxypropyl methylcellulose (HPMC), which is a known thickening agent. One skilled in the art would recognize that such an ingredient would not be used for injectable formulations. Consequently, this formulation is limited to an ocular composition for topical ophthalmic use only, as evidenced by Collier's disclosure that ophthalmic solutions contain thickeners such as HPMC (see page 6, lines 25-26). Furthermore, Collier teaches that the active ingredient present in topical ophthalmic suspensions or solutions is delivered in volumes of 1 to 2 drops per eye (see page 7, lines 4-9), which corresponds to 50 - 100 µl volumes (20 drops per ml) per eye. Thus, this formulation would deliver a dose of 50-100 µg of eliprodil to a subject. One skilled in the art would recognize that such amounts would have at best a local ocular effect, but would not be sufficient or effective for anesthetic or analgesic effect as claimed by the present invention.[1] Thus, Example 3 does not anticipate the invention, which requires a much higher dosage amount.

Collier's Example 6 also fails to teach the claimed invention. Example 6 discloses a 0.3% solution of 0.33% glutamate antagonist and 0.01% benzalkonium chloride solution. Again, this solution is limited to ophthalmic use only. Collier teaches that "compounds can also be delivered in ocular irrigating solutions used during surgery ... for irrigating solution formulations" (page 6, lines 12-14). Collier incorporates by reference U.S. Patent No. 5,604,244 (to DeSantis) (page 6, lines 12-14) which teaches that the "irrigating solutions of the present invention will typically contain one or

[1] This dosage amount would be administered where the subject is human or a large mammal. For smaller mammals, a corresponding appropriate reduction in volume would be administered. Therefore, one skilled in the art would recognize that the comparable lower volume for the smaller mammal would still not be sufficient for the anesthetic or analgesic effect. Accordingly, all mammals are covered.

more polyamine antagonists at a concentration of about 1 picomolar (pM) to about 1 millimolar (mM), preferably 0.1 nanomolar (nM) to 100 micromolar (μM), most preferably 1nM-10μM." (DeSantis, col. 5:lines 20-25). One skilled in the art would recognize that the dosage amounts from irrigation would be indeterminable, as the solution does not stay at the ocular site, but rather washes away. Therefore, again, the formulations would not be able to achieve the anesthetic or analgesic amounts as required by the claimed invention.

The effective dosages disclosed in Collier are distinguishable from the effective amounts claimed in the present invention. Particularly, Collier discloses formulations containing from 0.3% to 1% of a glutamate receptor antagonist with 0.015% benzalkonium chloride, for ocular administration. As a result, the total dose of NMDA receptor antagonist would be expected to be orders of magnitude lower than that effective to induce analgesia, much less anesthesia. In contrast, the present invention recites an anesthetically or analgesically effective amount of an NMDA receptor antagonist. Therefore, the formulations in Collier do not anticipate the claimed invention. Accordingly, applicants respectfully request the rejection be withdrawn.

IV. Rejection under 35 U.S.C. §103(a)

Claims 1 and 10-22 stand rejected as unpatentable under 35 U.S.C. 103(a) over GB 1330878 (Bristol Myers Squibb or BMS) in view of U.S. Patent No. 6,638,981 (to Williams). According to the Examiner, BMS teaches a composition of ketamine and benzethonium chloride. The Examiner relies on Williams to allege that benzalkonium chloride is an equivalent to benzethonium chloride. Further, the Examiner notes that although the references teach different dosage amounts for ketamine and benzalkonium chloride, one skilled in the art would be able to determine the claimed dosage amounts. Applicants respectfully traverse the rejection and request reconsideration.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. However, assuming *arguendo*, that a *prima facie* case of obviousness has been established, which applicants do not concede, Applicants have provided unexpected results to rebut a *prima facie* case. According to the Manual of Patent Examining Procedure (MPEP), evidence of unobvious or unexpected advantageous properties rebuts *prima facie* obviousness. MPEP 716.02(a). The presence of a property not possessed by the prior art is sufficient evidence of nonobviousness.

In re Papesch, 315 F.2d 381 (C.C.P.A. 1963). Applicants submit that based on the teachings of the present invention, the presently claimed invention clearly provides unobvious and unexpected results.

The present invention clearly discloses the known neurotoxic effect of ketamine compositions with benzethonium chloride as a preservative. (See pages 5-6 of the specification). Ketamine when tested alone did not exhibit the same neurotoxicity. However, when the preservative, benzethonium chloride, was tested alone, the neurotoxic effects were seen. (See pages 5-6 of the specification).

Examples 2 and 3 of the present specification demonstrate that a composition of ketamine and benzalkonium chloride as the preservative have little or no neurotoxicity. The control in the study was saline vehicle with comparisons to MK-801, a known neurotoxic NMDA receptor antagonist. The data in these Examples demonstrates that little to no neuronal vacuolization was present in the test composition of ketamine with benzalkonium chloride. If, in fact, all quaternary ammonium preservatives were interchangeable, one skilled in the art would expect benzalkonium chloride to have the same neurotoxic effect as shown for benzethenium chloride in the prior art. This difference between the claimed invention and the prior art was not obvious.

Applicants submit herewith a Declaration by Donna Madden pursuant to 37 C.F.R. § 1.132, providing evidentiary support to demonstrate that ketamine and benzethonium chloride exhibit neurotoxicity to a greater degree than a formulation of ketamine and benzalkonium chloride (*See* Madden Decl.). As such, the data clearly demonstrate how the preservatives benzethonium chloride and benzalkonium chloride are not interchangeable. (*Id.* ¶¶ 11-16). As noted by Ms. Madden, when a comparison between preservatives at the same dose, administered by the same route, was carried out to test neurotoxicity, the benzethonium chloride composition exhibited greater degenerative neuron incidence. (*Id.* ¶ 14). In fact, the data show a 2- to 4-fold increase in the incidence of neuron degeneration with benzethonium chloride as the preservative versus benzalkonium as the preservative, using the data from formulation test group 1 or the blended data from formulation test groups 1 and 2. (*Id.* ¶ 11).

Based on what is known in the art, and as compared to the data provided herein, applicants submit that the present invention has found that quaternary ammonium preservatives are not freely

interchangeable in the sense that the benzethonium chloride has a greater neurotoxic effect than benzalkonium chloride. Since there is a discoverable objective unexpected difference between the types of preservatives, the claimed invention cannot be obvious over the cited art. *See Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut prima facie obviousness even though there was no evidence that the compound was effective against all bacteria); *see also In re Papesch*, 315 F.2d 381, 137 USPQ 43 (C.C.P.A. 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound).

Furthermore, these data support the principle advanced in this application, that in compositions of NMDA receptor antagonists, the choice of preservative can have a significant impact on neurotoxicity. With no teaching in the prior art to select a preservative that yields a composition with reduced neurotoxicity, there was no basis for combining references in accordance with the Examiner's suggestion, nor any reasonable expectation that the combined references would, in fact, teach the claimed invention. The Examiner's logic would lead to a combination with benzethonium chloride, which Applicants teach, and here demonstrate, results in a composition with greater neurotoxicity. Consequently, the claimed invention is not obvious. Accordingly, Applicants request the rejection be withdrawn.

V. Double patenting

Claims 1 and 10-22 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-13 and 24-25 of copending application 10/256,283 ("the '283 Application"). The '283 Application, which is related to the present application, is currently pending. Since the rejection is provisional because the allegedly overlapping claims have not yet been patented, to the extent that claim scope overlaps in any patented case, Applicants will agree to submit a terminal disclaimer at such necessary time.

VI. Conclusion

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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